

3 WHAT IS CLAIMED IS:

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5 1. A method of modulating the expression of a nucleic  
6 acid in the hepatic system of a mammal, comprising  
7 the step of:

8 administering to said mammal an oligonucleotide  
9 which hybridizes to said nucleic acid to modulate  
10 the expression of said nucleic acid,

11 wherein said oligonucleotide has at least two  
12 sterol moieties covalently bonded thereto.

13

14 2. The method of claim 1, wherein said oligonucleotide  
15 is an antisense nucleotide.

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17 3. The method of claim 1, wherein at least one of said  
18 sterol moieties is a cholesteryl moiety.

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20 4. The method of claim 1, wherein said oligonucleotide  
21 comprises two cholesteryl moieties.

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23 5. The method of claim 1, wherein said sterol moieties  
24 are bound at the 2'-O, 3'-O or 5'-O positions of  
25 said oligonucleotide.

26

27 6. A method of preferentially targeting an antisense  
28 oligonucleotide to liver cells in a mammal,  
29 comprising the steps of:

30 covalently bonding said oligonucleotide to at  
31 least two sterol moieties to form a sterol-  
32 oligonucleotide conjugate; and

- 1           administering said sterol-oligonucleotide
- 2           conjugate to said mammal to preferentially target
- 3           said oligonucleotide to said liver cells in said
- 4           mammal to modulate the expression of a gene in said
- 5           liver cells.
- 6
- 7   7.    The method of claim 6, wherein said liver cells are
- 8           endothelial cells.
- 9
- 10   8.   The method of claim 6, wherein said oligonucleotide
- 11           is an antisense nucleotide.
- 12
- 13   9.   The method of claim 6, wherein at least one of said
- 14           sterol moieties is a cholesteryl moiety.
- 15
- 16   10.   The method of claim 6, wherein said oligonucleotide
- 17           comprises two cholesteryl moieties.
- 18
- 19   11.   The method of claim 6, wherein said sterol moieties
- 20           are bound at the 2'-O, 3'-O or 5'-O positions of
- 21           said oligonucleotide.
- 22
- 23   12.   A method of treating an animal having a hepatic
- 24           disease or disorder associated with a protein
- 25           encoded by a gene, comprising the step of:
- 26                administering to said mammal an oligonucleotide
- 27           which hybridizes to said gene,
- 28                wherein said oligonucleotide has at least two
- 29           sterol moieties covalently bonded thereto.
- 30
- 31   13.   The method of claim 12, wherein said oligonucleotide
- 32           is an antisense nucleotide.
- 33

1 14. The method of claim 12, wherein at least one of said  
2 sterol moieties is a cholesteryl moiety.

4 15. The method of claim 12, wherein said oligonucleotide  
5 comprises two cholesteryl moieties.

7 16. The method of claim 12, wherein said sterol moieties  
8 are bound at the 2'-O, 3'-O or 5'-O positions of  
9 said oligonucleotide.

11 17. A composition, comprising an oligonucleotide,  
12 wherein said oligonucleotide has at least two  
13 sterol moieties covalently bonded thereto.

15 18. A composition, wherein said oligonucleotide is an  
16 antisense nucleotide.

18 19. The composition of claim 17, wherein at least one of  
19 said sterol moieties is a cholesteryl moiety.

21 20. The composition of claim 17, wherein said  
22 oligonucleotide comprises two cholesteryl moieties.

24 21. The composition of claim 17, wherein said sterol  
25 moieties are bound at the 2'-O, 3'-O or 5'-O  
26 positions of said oligonucleotide.

28     22. The composition of claim 17, wherein said  
29     oligonucleotide hybridizes to a gene encoding a  
30     protein that is overexpressed or abnormally  
31     expressed in hepatic tissues in the course of a  
32     disease or a disorder.